# New β-lactams to inhibit the Fatty Acid Amide Hydrolase (FAAH)


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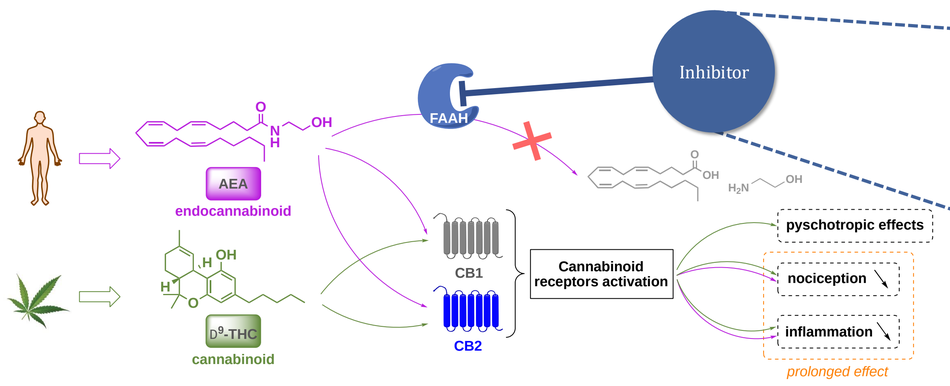
## Introduction

Anandamide (AEA) is an endogenous agonist of the endocannabinoid receptors (CB1 and CB2) which are highly interesting targets for medicinal applications in the fields of pain and CNS disorders. The levels of AEA in the body are controlled by the Fatty Acid Amide Hydrolase (FAAH).

Inhibiting FAAH for prolonging the activation of CB1 and CB2 has thus a clear therapeutic potential. The search for selective inhibitors of FAAH has already produced active compounds and remains an active and growing field.

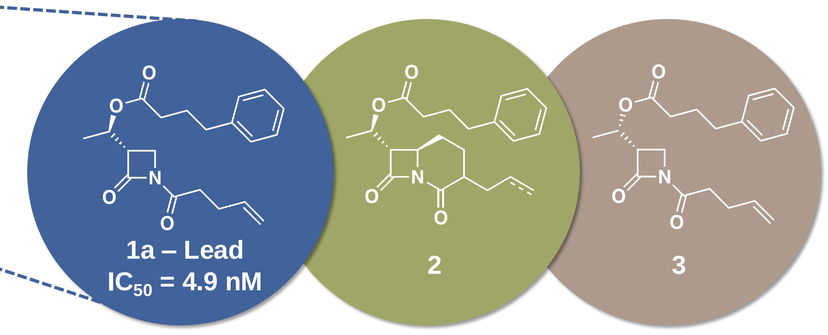



## Objectives

Our lead compound **1a**, featuring an original β-lactamic structure, exhibits a nanomolar activity ($IC_{50}$ = 4.9 nM) and a fully reversible mode of action on FAAH. It was also shown to be selective toward FAAH compared to the monoacylglycerol lipase (MAGL).

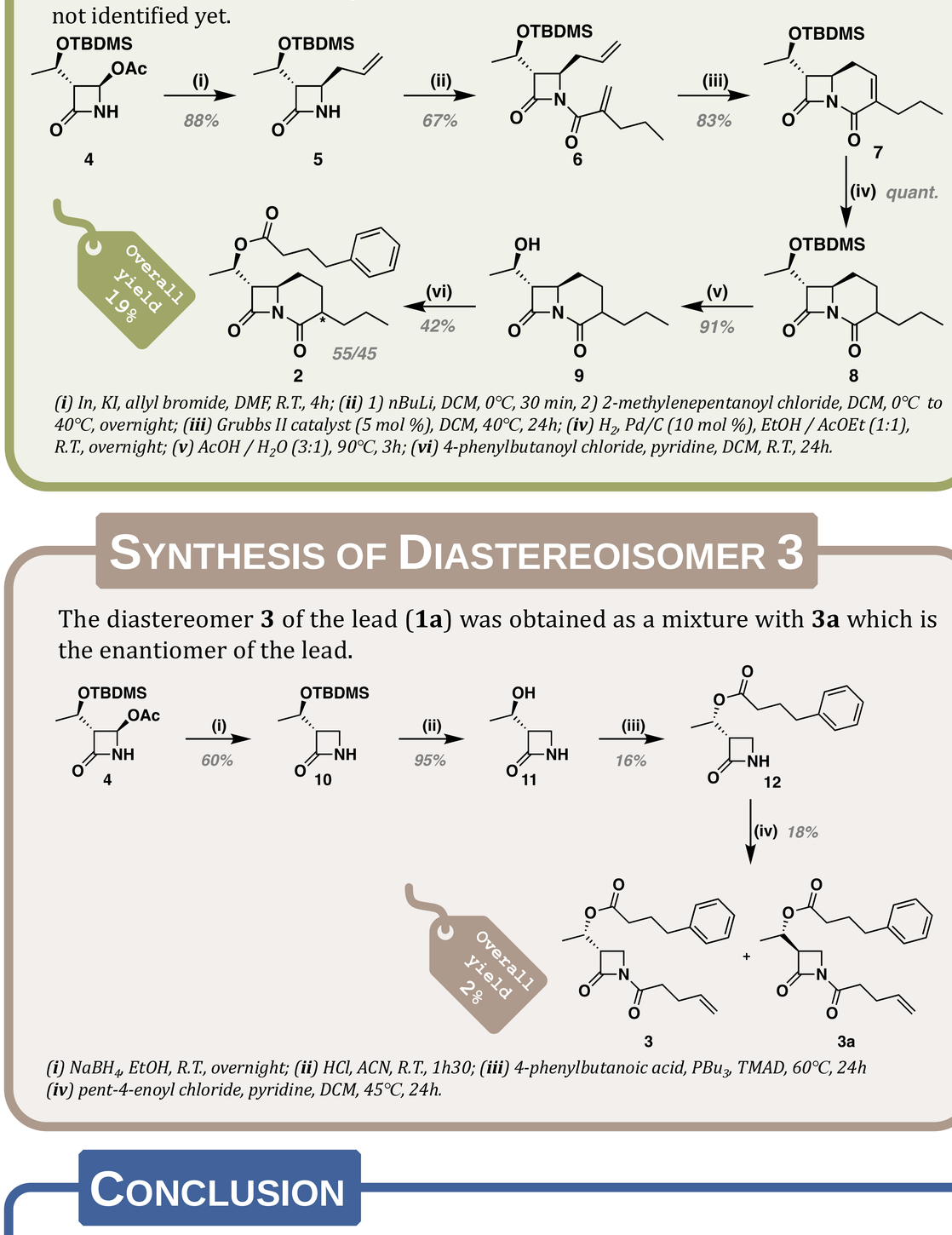
The goals of this project are

(1) to explore the influence of the imide conformation (see **2**),
(2) to investigate the influence of the chirality induced by the methyl group at the C5 position (see **3**);




## Synthesis of Bicycle 2

Both diastereoisomers of the bicycle **2** (**2a** and **2b**) were obtained in six steps with a ratio of 55/45 and an overall yield of 19%. The diastereoisomers were isolated but are not identified yet.




*(**i**) In, KI, allyl bromide, DMF, R.T., 4h; (**ii**) 1) nBuLi, DCM, 0°C, 30 min, 2) 2-methylenepentanoyl chloride, DCM, 0°C to 40°C, overnight; (**iii**) Grubbs II catalyst (5 mol %), DCM, 40°C, 24h; (**iv**) $H_2$, Pd/C (10 mol %), EtOH / AcOEt (1:1), R.T., overnight; (**v**) AcOH / $H_2O$ (3:1), 90°C, 3h; (**vi**) 4-phenylbutanoyl chloride, pyridine, DCM, R.T., 24h.*

## Synthesis of Diastereoisomer 3

The diastereomer **3** of the lead (**1a**) was obtained as a mixture with **3a** which is the enantiomer of the lead.




*(**i**) $NaBH_4$, EtOH, R.T., overnight; (**ii**) HCl, ACN, R.T., 1h30; (**iii**) 4-phenylbutanoic acid, $PBu_3$, TMAD, 60°C, 24h (**iv**) pent-4-enoyl chloride, pyridine, DCM, 45°C, 24h.*

## Conclusion

Three bicycles (**2a**, **2b** and **2c**) were synthesized. We found that these molucles have a good inhibitor activity. Moreover, it was observed that the strerochemisty of the carbon bearing the propyl has a significant influence on the activity.

The enantiomer of the lead (**3a**), a 1:1 mixutre of the diastereoisomer of the lead (**3**) and **3a** were obtained. Surprinsingly, it was shown that the stereochemistry has only a minor influence on the inhibitor activity.

These new results still have to be included in our docking studies.

## References


- M. Feledziak, C. Michaud, A. Urbach, D. M. Lambert, J. Marchand-Brynaert, *J. Med. Chem.*, **2009**, *52*, 7054-7068.
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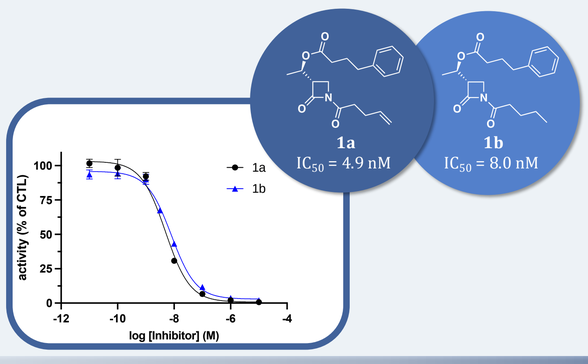
- A. Morelle, J. Caruano, M. Feledziak, C. Michaux, E. A. Perpete, G. G. Muccioli, J. Marchand-Brynaert, R. Robiette, *Chimie nouvelle*, **2020**, *134*, 41-49.


## Acknowledgments

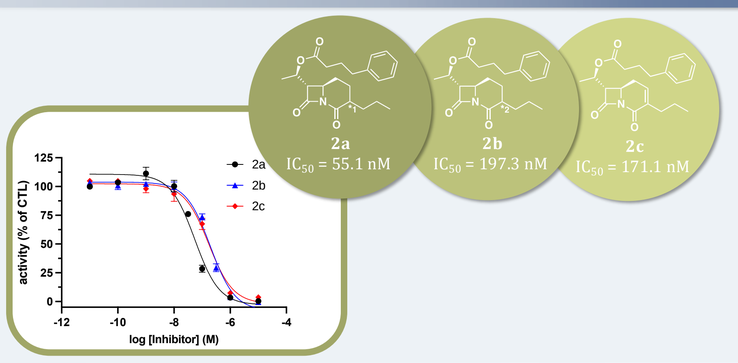

Catherine Michaux and Eric Perpete are gratefully acknowledged for the docking studies as well as Juhans Dechenne for his help for the synthesis of the bicycles.


## Pharmacological Evaluation

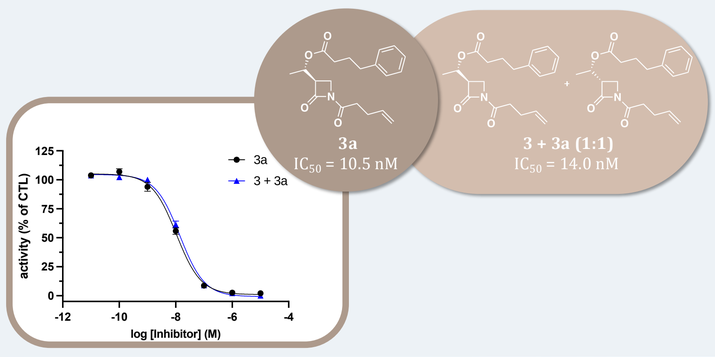
The $IC_{50}$ determination was perfomed in triplicate on a mouse brain homogenate.




✓ $IC_{50}$ of **1a** and **1b** are quite similar.
✓ It seems that the double bond has no significant influence on the inhibition of the FAAH.




✓ One of the two diastereoisomers (**2a**) is really more active than the other one (**2b**).
✓ The third bicycle with the α,β-insaturation (**2c**) has a similar activity than **2b**.




✓ The enantiomer of the lead **3a** has a good inhibition activity.
✓ The 1:1 mixture of **3** and **3a** gives a similar $IC_{50}$ just a bit higher than **3a** alone suggesting that **3** has a similar activity than **3a**.

## Docking Studies

The docking studies were performed by C. Michaux and E. Perpete from University of Namur (Belgium).
As the 3D structure of human FAAH has not been determined by X-ray diffraction, the study was performed on humanised rat FAAH structure.
The modeling give some interseting results :

✓ The phenyl of **1a** is located in the phenyl pocket
✓ The methyl is located in the hydrophobic pocket
✓ Both carbonyls of imide interact *via* hydrogen bonds with serine residues of the catalytic triade
✓ A molecule of water is involed in the interaction.

New results reported on this poster still need to be included in this docking study.